



OTSUKA AMERICA PHARMACEUTICAL, INC.

2440 Research Boulevard, Rockville, Maryland 20850
Telephone (301) 990-0030 Telefax (301) 990-0036

September 17, 2000

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Dockets Management Branch (HFA-305)
Food and drug Administration
5630 Fishers lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 94D-0325 and 96D-0009

Dear Sirs:

Following are the comments from Otsuka America Pharmaceutical Inc. (OAPI) on the International Conference on Harmonisation: Draft Revised Guidance Q3A(R), Impurities in New Drug Substances and Q3B(R), Impurities in New Drug Products.

Both draft guidances now allow for rounding of significant digits. The rounding may effectively increase allowable unqualified and unidentified impurity levels in the drug substances and degradation products in the drug product. For example, in Q3A(R) for a drug substances with a daily dose greater than 2grams, an impurity level of 0.149% will now be rounded down to 0.1%. However, the guidance sets the qualification and identification threshold at greater than 0.1%. Therefore, since the rounded down figure does not exceed the allowable 0.1% limit the impurity may not be identified or qualified. In this instance, rounding may result in an increase of up to 49% of an unidentified and unqualified impurity in the drug substance.

We trust that the Expert Working Groups for both Q3A and Q3B guidances have taken the toxicological and quality impact of this potential increase in unqualified and unidentified impurity and degradation product levels into consideration.

Please feel free to contact me at (301) 527-4701 should you need additional information or clarification.

Sincerely yours,

Suva B. Roy, Ph.D.
Senior Director, Regulatory Affairs CMC

96D-0009

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